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Review Article

Dentistry Section

Multifactorial Relationship of Obesity and Periodontal Disease

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ABSTRACT

Obesity is a chronic disease of mutifactorial origin, where there is increase in body fat. Periodontitis is an inflammatory disease of tooth supporting tissues resulting in destruction of periodontal ligament and alveolar bone. Periodontitis and obesity are both chronic health problems and the literature supports this association. A hyperinflammatory state observed in obesity is proposed as a mechanism to explain this association. This low grade inflammation in obese subjects triggers the worsening of non transmissible chronic diseases like periodontitis. So the aim of this article is to get the overview of association between adipose tissue derived cytokines and periodontal disease.

Keywords: Obesity, Adipokines, Periodontal disease

INTRODUCTION

Obesity and overweight are the most common nutritive disorder associated with increased mortality and morbidity of cardiovascular disease. Obesity is an excess amount of body fat in proportion to lean body mass, to the extent that health is impaired [1]. Obesity represents a condition wherein the proper sensing and management of nutrients and energy status present significant challenges at cell and organism levels. Recently it is suggested that some form of obesity is associated with chronic low grade infection. Periodontitis is inflammation of the periodontium leading to destruction of connective tissue attachment of teeth. Periodontal disease is no longer identified as only an oral health problem but also a public health issue as it is associated with systemic health. Continuous bacterial challenge in periodontitis leads to low grade chronic infection which exacerbate the ongoing inflammation in distant organs. Obesity represents the systemic condition capable of influencing the onset and progression of periodontal disease. The adipose tissue has been shown to function as endocrine organ which secretes numerous factors referred as adipocytokines and can cause disease through dysregulated immune responses [2].

MEASURES OF OBESITY

A crude population measure of obesity is the body mass index (BMI) which is calculated by dividing a person's weight in kilograms by the square of the height in meters (kg/m^2). The normal range is 19–24.9 kg/m^2, with overweight defined as 25–29.9 kg/m^2, and obesity as ≥30 kg/m^2. Since BMI cannot assess the regional body fat distribution, waist circumference, can also be used to determine the valid index of visceral fat accumulation. A waist circumference of greater than 102 cm in men and 88 cm in women is a risk factor for Cardiovascular disease. Waist circumference represents the correlation with the amount of visceral adipose tissue which is more active and secrete greater amount of cytokines and hormones.

WHO reported that over 200 million men and 300 million women were obese [3]. In India 5% people were affected with obesity. Since Asians experience obesity related diseases at lower body mass indices, new criteria of overweight for Asians is BMI of ≥23. Following this criteria, the number of adults who are overweight is closer to 1.7 million [4].

Adipokines – Key Player in Obesity and Periodontal Disease

Human adipose tissue is divided into brown adipose tissue and white adipose tissue. The brown adipose tissue has multilocular adipocytes with abundant mitochondria, responsible for thermogenic activity of the tissue and the white adipose tissue is responsible for fat storage. White adipose tissue consists of different cell types like fibroblasts, preadipocytes, mature adipocytes and macrophages. Normally adipose tissue is populated by 5-10% macrophages, but obesity results in 60% macrophage infiltration in adipose tissue. Adipose tissue was thought as an inert organ for many years and currently adipose tissue is considered as a complex and metabolically active endocrine organ that secretes numerous immunomodulatory factors. Adipocytes secrete bioactive molecules called adipokines which can act locally or systemically as signalling molecules to liver, muscle and endothelium [5]. Adipokines are soluble proteins that bind receptors on target cells and initiate intercellular signalling cascades resulting in phenotypic changes to the cell through altered gene expression and regulation. They play as different roles like classical hormones (eg.tumor necrosis factor-α), hormone like proteins (e.g. leptin, resistin), proteins involved in vascular hemostasis and angiotensin. These adipocytokines activate monocytes which increases the production of inflammatory cytokines thus playing an important role in initiation of periodontal disease. Insulin resistance also mediates the relationship between obesity and periodontal disease. In obesity, insulin resistance may occur due to increase in tumor necrosis factor-α, (TNF-α) levels suppress insulin induced tyrosine phosphorylation of insulin receptor substrate -1 and blocks translocation of glucose transporting protein thereby impairing insulin action [5].

Numerous studies reported the association of obesity with elevated systemic C-reactive protein, which is a marker of low grade inflammation. This obesity related low grade inflammation triggers the occurrence of periodontal disease. The relationship between obesity and periodontal disease was first reported by ResMI and Bissada NF [6]. They reported the histopathological changes in the periodontium of obese Zucker rats in addition to greater alveolar bone resoption when compared to non-obese rats. The meta-analysis of the systematically identified results from 57 independent study populations suggested an approximate one-third increase in

the prevalence odds of obesity among subjects with periodontal disease [7].

Leptin was the first adipocyte hormone discovered, which is a 16 kDa non-glycosylated peptide hormone mainly produced by adipocytes and in minor quantities by placenta, T-cell, osteoblast and gastric epithelium. Plasma leptin level decreases during fasting, induces the neural pathways in hypothalamus to increase the appetite and decrease the energy expenditure as the body attempts to restore the energy store. Leptin controls food intake within brain-gut axis, provides a satiety signal through its action on central nervous system receptors within the hypothalamus. Recent evidence showed that leptin enhances the host immune mechanism by activation of monocytes and macrophage function and orchestrate activities like phagocytosis and cytokine production, chemotaxis and oxidative species production by stimulated neutrophils, development of natural killer cells and shifting T-cell responses towards Th1 cytokine type and inhibit Th2 cell, induction of expression and secretion of interleukin-1 receptor antagonist by monocytes in vitro suggesting an anti-inflammatory action of leptin. The leptin receptor is homologous to glycoprotein-130, the signalling transduction subunit of interleukin-6 (IL-6) family cytokines which are important mediators of acute phase reactant protein (APR). Thus the overall increase in leptin during infection and inflammation indicates that leptin is part of immune response and host defense mechanisms. Leptin is also involved in two different bone controlling mechanism either by producing direct stimulatory effect on bone growth like osteoblast proliferation, differentiation and prolonging the life span of osteoblasts by inhibiting apoptosis or producing indirect suppressive effect on bone through hypothalamus. Karthikeyan and Pradeep AR have shown that leptin is present in healthy gingiva and leptin concentration reduced coincident to severity of inflammation [8]. The same author also reported that serum leptin levels are increased in periodontitis [9]. From this varied results, it can be speculated that secreted leptin may be used as substrate during inflammation.

Adiponectin is a product of adipocytes and its levels decrease in obese subjects. There are two types of adiponectins, a full length adiponectin and a globular adiponectin and the major receptors for adiponectin are AdipoR1 and AdipoR2. AdipoR1 is a high affinity receptor for globular adiponectin. AdipoR2 is an intermediate affinity receptor for globular adiponectin and full length adiponectin. Adiponectin has several beneficial effects like anti inflammatory, vasoprotective and antidiabetic effects. These protective effects occur due to suppression of tumor necrosis factor-α, interleukin-6 and along with induction of interleukin-1 receptor antagonist. Iwayama et al showed that adiponectin has potent beneficial function to maintain the homeostasis of periodontal health, improve periodontal lesion and contribute wound healing and periodontal regeneration [10]. Yamaguchi et al., reported that adiponectin may not function efficiently in sites of periodontal disease because of decrease in the number of receptors and this dysfunction may play role in worsening periodontitis [11].

Resistin belongs to secretory protein family called as resistin like molecules, which is characterized by a highly conserved cysteine rich C- terminal. Resistin has been named since it is believed to convey the resistance to insulin. Resistin may not originate directly from adipocytes but may originate from inflammatory cells infiltrating the fat tissue. Release of resistin appears to be stimulated by inflammation, LPS, IL-6, hyperglycemia, growth and gonadal hormones. While released within the fat tissue, resistin acts on adipocytes leading to insulin resistance. Levels of resistin increase with increasing obesity which is a major contributing factor for the development of type 2 diabetes mellitus, and periodontitis. Devanoorkar et al., reported that the decrease in serum resistin levels following nonsurgical periodontal therapy did not show any statistical significance [12]. Two studies showed the positive association of periodontal disease with gingival crevicular fluid(GCF) resistin levels [13,14].

Visfatin is the most recently identified adipocytokine produced by visceral adipose tissue and has insulin-mimetic action. Visfatin, also known as nicotinamide phosphoribosyl transferase (NAMPT), which was previously known as a pre-B cell colony-enhancing factor (PBEF), functions as a growth factor for early B cells within the immune system. Concentrations of visfatin are increased in abdominal obesity and diabetes mellitus, which could be due to visfatin's compensatory attempt to maintain blood euglycemia. Visfatin binds to insulin receptor at a site distinct from insulin and exerts hypoglycaemic effect. Visfatin was identified in inflammatory cells and their levels were elevated in various inflammatory conditions like periodontitis. Nogueira et al., in his study reported that the oral microorganisms seem to stimulate visfatin synthesis, suggesting a possible pathogenic role for this adipokine in periodontal diseases. [15] Pradeep and Raghavendra showed the positive association of GCF visfatin concentration in chronic periodontitis subjects [16,17]. They concluded that the visfatin values can be considered as an inflammatory marker and can be explored in future as a potential therapeutic target in the treatment of periodontal disease.

Chemerin is known as tazarotene-induced gene 2 (TIG2) or retinoic acid receptor responder 2 (RARRES2). It is a potent chemoattractant for chemokine like receptor-1 (CMKLR1) expressing cells. Chemerin circulates in blood as prochemerin. Angiotensin converting enzyme may be responsible for the conversion of prochemerin. Platelets are the rich source of chemerin. Recently it has been reported that the adipocytes and fibroblasts secrete chemerin. Chemerin functions like chemokine and induces leukocyte migration and intracellular calcium mobilization. Plasma chemerin levels in normal subjects are significantly associated with body mass index, circulating triglycerides, and blood pressure, suggesting a strong relationship of this protein with obesity-associated complications. In addition to serving as a bridge between innate and adaptive immunity via chemotaxis of dendritic cells and macrophages, chemerin may also play a role in obesity, diabetes, psoriasis and tumor biology [18].

Omentin, which was originally referred to as intelectin and first found in the intestinal Paneth cells, has a predicted molecular weight of 33 kDa. Omentin is a fat depot-specific secretory protein synthesized by the visceral stromal vascular cells, but not the adipocytes. It has also been found in the human lung, intestine, and heart and is strongly expressed in the human ovaries and placenta.

Apelin is another short peptide released from adipocytes upon stimulation. Apelin exists in at least three forms, consisting of 13, 17, or 36 amino acids, all originating from a common 77-amino-acid precursor. Apelin synthesis is stimulated by insulin and plasma apelin levels increased in obesity associated insulin resistance and hyperglycemia.

No studies available to show the association of chemerin, omentin and apelin with periodontal disease.

Role of Oral Bacteria in Obesity

Infectobesity the term coined by Dr. Nikhil refers to obesity of infectious origin. This concept was accepted since the gut bacteria extract their needful diet more from obese individual compared to lean individuals. Goodson et al., suggested three mechanisms, for the role of oral bacteria in the development of obesity [19]. First, oral bacteria may increase metabolic efficiency, as suggested by infectobesity proponents. The second hypothesis is that oral bacteria could increase weight gain by increasing appetite. The third hypothesis is that oral bacteria redirect energy metabolism by facilitating insulin resistance through increasing levels of tumor necrosis factor-α (TNF-α). Using any of these mechanisms, even a small excess in caloric consumption with no change in diet or exercise could result in unacceptable weight gain. Periodontal disease may contribute to the development of obesity and the role of the oral microbiota in obesity has been gaining more attention. Studies have shown that obesity is also associated with increased

counts and proportions of certain periodontal pathogens, including *Tannerella forsythia* and *Selenomonas noxia* [20].

Oxidative Stress and Obesity

Oxidative stress is involved in many pathologic conditions like obesity, diabetes and cardiovascular disease. In obesity, the organism cannot adapt and maintain homeostasis under continuous energy and nutrient exposure, and the consequent emergence of metabolic and oxidative stress leads to inflammatory responses and cell organelle dysfunction. Adipocytokines are also responsible for production of reactive oxygen and nitrogen by macrophages and monocytes leading to increased oxidative stress. Angiotensin II secreted by adipocytes stimulate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity. NADPH oxidase is responsible for ROS production in adipocyte.

Obesity increases the mechanical load and myocardial metabolism, therefore oxygen consumption is increased. Increased oxygen consumption leads to increased ROS production derived from increase in mitochondrial respiration. The effect of high triglyceride (TG) affects functioning of the mitochondrial respiratory chain, inhibits translocation of adenine nucleotides and promotes the generation of superoxide [21].

Interventions in Obese Subjects

Several methods have been proposed for weight loss in obese patients, including dieting and physical activity, pharmacologic treatment and surgical intervention. A recent systematic review concluded that bariatric surgery (BS) is a clinically and cost effective intervention for moderate to severe obese subjects compared with nonsurgical intervention [22]. Two types of operations performed. Banded gastrotrophy restricts the gastric volume and Roux-en-Y gastric bypass which limits food intake. After bariatric surgery, food and salivary secretions go directly into the distal jejunum, bypassing the duodenum and the proximal jejunum. This bypass produces its effect on satiety, reducing food intake and body weight by modulation of neural and hormonal responses. Schauer et al., suggested that BS is a successful treatment for type 2 diabetes as well as reduction of inflammatory mediators such as tumor necrosis factor-α, interleukin-6 and leptin after surgery [23]. The reduction in proinflammatory cytokines secondary to weight loss may have an indirect effect on periodontal health. Lakkis et al., reported an improved response to non-surgical periodontal therapy observed in obese patients who had significant weight loss after bariatric surgery compared to obese patients who did not have such a surgery [24]. Pataro et al., also observed the differences in periodontal condition in individuals at different times of the bariatric surgery, showing a high prevalence of periodontitis in both preoperative and postoperative follow-up [25].

CONCLUSION

Excessive storage of adipose tissue in obese individuals leads to the release of adipokines which have biologic functions. Prevention of obesity can be done by advising lifestyle changes and prescribing balanced diet to control body weight. Maintaining good oral health is also fundamental for obese individuals. Dental practitioners should educate their obese patients about the risk of periodontal disease and reinforce the importance of proper oral hygiene.

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